PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Wen-Tien Chen	Examiner:	Unassigned
Serial No.:	10/727,211	Group Art Unit:	Unassigned
Filed:	December 3, 2003	Docket:	178-295 CIP/CON
For:	COMPOSITIONS AND METHODS FOR INHIBITION OF CANCER INVASION AND ANGIOGENESIS	Dated:	February 6, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify this correspondence is being deposited with the United States Postal Service as first class mail, postpaid in an envelope, addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313 on February 6, 2004
Signature: Julie L. Watts

DECLARATION UNDER 37 C.F.R §1.132

Sir;

I, Wen-Tien Chen, Ph.D., declare as follows:

1. I received a Ph.D. in Genetics and Cellular and Developmental Biology from Yale University in 1979.

2. Since 1982, I have held faculty positions at a number of accredited universities, including the Howard University Cancer Center at Howard University College of Medicine, the Department of Cell Biology at Georgetown University School of Medicine, and the Lombardi Cancer Center at Georgetown University School of Medicine.

3. Currently, I am a professor in the Department of Medicine/Division of Neoplastic Diseases at the State University of New York at Stony Brook. In addition, I am the director for the Program of Angiogenesis and Metastasis at the Long Island

Cancer Center at the State University of New York at Stony Brook. Furthermore, I am founder and president of Vitatex Inc., Stony Brook, New York.

4. I served as a committee member for the National Institutes of Health in review panels for the Biomedical Sciences Study Section from 1984 to1987 and the Cell Biology Study Section from 1989 to 1993.

5. For various periods from 1984 to 2003, I served as an ad hoc committee member for the following: Tumor Progression and Metastasis Study Section; National Institutes of Health, Pathology B Study Section; NCI Special Emphasis Panel ZCA1 SRRB-C Study Section; Cancer Center Support Grants, site visits; National Cancer Institute Cancer Preclinical Program Project Review Committee, site visits; National Cancer Institute Special Review Committee, Outstanding Investigator Grants; national Institutes of Health Special Review Committee; RFA De-98-008 Genetic Mechanisms in Oral Cancer; RFA 86-HL-30-L Fibroblast Heterogeneity in Pulmonary Fibrosis; and National Pathology B Study Section, Special Study Section Review.

6. I am an author of over twenty peer-reviewed publications concerning cancer invasion and angiogenesis.

7. I am an expert in the field of cancer invasion and angiogenesis as evidenced by my curriculum vitae, which is attached as exhibit 1.

8. I am the sole inventor of the above-identified U.S. patent application Serial No: 10/727,211 titled "Compositions and Methods for Inhibition of Cancer Invasion and Angiogenesis."

9. The experiments described in exhibits 2 and 3 were performed by me or by persons directly under my supervision and control.

10. The cited art (i.e., Duke- Cohan et al.) report binding of anti-DPPIV (dipeptidyl peptidase IV) antibodies to activated T cells. It is well known to those skilled in the art that DPPIV is also referred to as CD26. Further, it is well know to those

skilled in the art that activated T cells express CD69. Thus, in the experiment described in exhibit 2, I investigated whether the epitope recognized by monoclonal antibodies E19 and E26 (both directed to DPPIV) are present on $CD69^+$ T cells. Monoclonal antibodies E19 and E26 are recited in the specification and claims.

11. In the experiment presented in exhibit 2, cells were isolated from bone marrow. The isolated cells were characterized by staining with fluorescently labeled antibodies to human CD69, control monoclonal antibody E3 (directed against DPPIV), and monoclonal antibody E19. After labeling, the cells were examined by fluorescent microscopy.

12. Similar to that reported in Duke-Cohan et al., Figure 1A of exhibit 2 demonstrates that the control monoclonal antibody E3 (directed against DPPIV) bound to activated ($CD69^+$) T cells. Therefore, the control monoclonal antibody E3 directed against DPPIV recognizes DPPIV present on $CD69^+$ T cell.

13. However, cells stained with monoclonal antibody E19 (directed against DPPIV) revealed a different staining pattern to that observed for monoclonal antibody E3 (see above paragraph 12). Unlike monoclonal antibody E3, monoclonal antibody E19 did not bind to $CD69^+$ T cells (see Figures 1B and 1C of exhibit 2). In addition, cells recognized by monoclonal antibody E19 were not recognized by anti-CD69 antibodies. Thus, the epitope recognized by E19 is not present on $CD69^+$ T cells. Therefore, monoclonal antibody E19 recognizes an epitope of DPPIV not present on activated ($CD69^+$) T cells.

14. Similar results were obtained for monoclonal antibody E26. Specifically, the epitope recognized by E26 is not present on $CD69^+$ T cells. Therefore, monoclonal antibody E26 recognizes an epitope of DPPIV not present on $CD69^+$ T cells.

15. The data presented demonstrate that monoclonal antibodies E19 and E26 do not bind $CD69^+$ T cells (i.e., activated T cells). As mentioned above, unlike

monoclonal antibodies E19 and E26, the monoclonal antibody to E3 and the monoclonal antibody to DPPIV in the cited art bind to activated (i.e., $CD69^{+}$) T cells. Therefore, the epitope recognized by monoclonal antibodies E19 and E26 are different from the epitope recognized by the monoclonal antibody E3 and the monoclonal antibody to DPPIV in the cited art.

16. DPPIV has been reported to be an adhesion receptor for fibronectin (see cited art of Cheng et al., Johnson et al., Abdel-Shany et al. and Elble et al.). In the cited art, monoclonal antibodies to DPPIV have been reported to inhibit binding of DPPIV to fibronectin. The reported inhibition of binding has been reported to inhibit adhesion and spreading of cells. Therefore, in the experiment described in exhibit 3, I investigated the ability of monoclonal antibodies E19 and E26 to inhibit spreading and attachment of W138 human embryonic fibroblasts on a fibronectin-coated collagen substratum.

17. Human embryonic fibroblasts cells WI38 were seeded, coated with rat tail type I collagen, and further coated with bovine serum fibronectin. The WI38 cells were seeded with monoclonal antibody E19 (directed against DPPIV), negative control monoclonal antibody C37 (directed against gp-90) and positive control monoclonal antibody C27 (directed against β1 integrins).

18. As expected, the negative control monoclonal antibody C37 (anti-gp-90) did not inhibit cell spreading and adhesion. However, as expected, the positive control monoclonal antibody C27 (against β1 integrins) inhibited WI38 cell spreading and adhesion on fibronectin-coated collagen substratum.

19. The data demonstrate that addition of monoclonal antibody E19 did not inhibit cell spreading (see figure 2A of exhibit 3) and attachment (see figure 2B of exhibit 3) of WI38 cells on fibronectin-coated collagen substratum. Therefore, the data indicates that monoclonal antibody E19 does not inhibit binding of DPPIV to fibronectin.

20. Similar results were obtained for monoclonal antibody E26. Specifically, monoclonal antibody E26 did not inhibit cell spreading and attachment of WI38 cells on fibronectin-coated collagen substratum. Therefore, monoclonal antibody E26 does not inhibit binding of DPPIV to fibronectin.

21. Therefore, from the experiment presented in exhibit 3 and figure 2, E19 and E26 do not inhibit binding of DPPIV to fibronectin. Unlike monoclonal antibodies E19 and E26, the antibodies to DPPIV in the cited art inhibit binding of DPPIV to fibronectin. Thus, the epitope recognized by E19 and E26 differs from the epitope recognized by anti-DPPIV antibodies in the cited art.

I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or nay patent issued thereon.

Respectfully Submitted,

Dated: 2/6/2004

Wen-Tien Chen, Ph.D.

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Wen-Tein Chen, Ph.D.

Professor
Department of Medicine/Division of Neoplastic Diseases
State University of New York
Stony Brook, New York

EDUCATION:

Bachelors of Science degree in 1968 from Tunghai University in Taiwan in field of biology.

Masters of Science degree in 1974 from Northeastern University in Massachusetts in field of embryology.

Doctorate of Philosophy degree in 1979 from Yale University in Connecticut in field of genetics, cellular and developmental biology.

POSITIONS AND HONORS:

1974-1979	Research Assistant, Biology Department, Yale University. (with Dr. J.P. Trinkaus).
1979-1982	Postdoctoral Fellow in the area of membrane chemistry, University of California at San Diego. (with Dr. S.J. Singer).
1982-1984	Director, Cytochemistry Division, Howard University Cancer Center; Assistant Professor, Department of Oncology, Howard University College of Medicine.
1984-1991	Associate Professor, Department of Cell Biology, Georgetown University School of Medicine.
1988-1992	Director, The Cytochemistry & Morphology Core, Lombardi Cancer Center. Georgetown University School of Medicine.
1988-8/1998	Director, Program of Cellular Control of Invasion and Metastasis, Lombardi Cancer Center, Georgetown University School of Medicine.
1992-1993	Sabbatical in Section of Molecular Biology, NIDR, NIH (Dr. Yoshi Yamada).
1992-1998	Professor, Department of Cell Biology, Georgetown University School of Medicine.
8/1998-	Professor, Department of Medicine/Division of Neoplastic Diseases, SUNY @ Stony Brook.
8/1998-	Director, Program of Angiogenesis and Metastasis, Long Island Cancer Institute, SUNY @ Stony Brook.
2001-	Founder & President, Vitatex Inc., a Long Island High Tech Incubator (LIHTI) company at Stony Brook, NY.

REVIEW PANELS:

(1). Committee Member:

National Institutes of Health, Cell Biology Study Section (CBY-1), 1989-1993;
National Institutes of Health, Biomedical Sciences Study Section (BI3), 1984-1987.

(2). Ad Hoc Committee Member:

Tumor Progression and Metastasis Study Section (TPM) 10/8-10/2003;
National Institutes of Health, Pathology B Study Section (PATHB), 6/3-6/2003;
NCI Special Emphasis Panel ZCA1 SRRB-C (O2) Study Section 07/30/2003;
Cancer Center Support Grants, Site Visits in 2/12-2/14/02; 10/11–10/13/00; 5/31-6/2/2000; 6/29–7/1/98, 10/6-10/8/97;
NCI Cancer Preclinical Program Project Review Committee, Site Visits in 1/23/2003; 2/28-3/2/99, 9/16-9/18/96, 1/23-1/25/96;
NCI Special Review Committee, Outstanding Investigator Grants: 12/9-12/11/92;
NIH Special Review Committee: 1/31-2/2/99, 3/1991, 3/1990, 3/1987;
RFA DE-98-008 Genetic Mechanisms in Oral Cancer, 1/31–2/2/1999;
RFA 86-HL-30-L Fibroblast Heterogeneity in Pulmonary Fibrosis, 7/8-7/9/1987;
NIH Pathology B Study Section, Special Study Section Review in 4/1984.

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2. Chen, W.-T. 1981. Mechanism of retraction of the trailing edge during fibroblast movement. J. Cell Biol. 90:187-200.
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EXHIBIT 2

Monoclonal antibodies E19 and E26 that recognize the DPPIV form (complex with seprase) do not share epitope with monoclonal antibodies directed against T-cell activation antigen CD26 or CD69.

CD26 and CD69 are T cell activation antigens. Cells enriched from bone marrow were characterized using: green fluorescent fluorescein isothiocyanate (FITC)-conjugated mouse anti-human CD69 monoclonal antibody FN50 (BD PharMingen, San Diego, panel marked Cd69); red fluorescent TRITC-conjugated rat anti-human DPPIV (i.e., anti-CD26) monoclonal antibody E3 (panel marked E3 Dp4); and bright blue-fluorescent Hoechst nuclear stains (panel marked Cd69+E3+nuclei). Note that blue-fluorescent Hoechst 33258 dye was used to image nuclei (Hs+) of cells.

After labeling, the cells were analyzed by microscopy. Microscopic identification of T-cell activation antigen CD69-positive leukocytes in a monoclear fraction of bone marrow cells shows that anti-CD69 antibody co-localize with anti-DPPIV (anti-CD26) antibody E3 (arrows) (see figure 1A). A CD69-positive T cell is identified by arrows and shown in the composite-triple color image in the right panel displaying CD69+ (green), E3+ (red), and nuclear stains (blue) fluorescence. Thus, DPPIV is present on activated T cells expressing CD26.

However, microscopic identification of activated T-cells labeled with anti-CD69 antibody (FN50) were not labeled with anti-DPPIV-seprase antibody E19 (arrows) (see figure 1B and 1C). The cells were prepared and stained with similar methods as in figure 1A, except that red fluorescent TRITC-conjugated rat anti-human DPPIV-seprase monoclonal antibody E19 (panel marked E19 Dp4) was used. A field adjacent to panel B of figure 1 showed a cell that was positively labeled with anti-DPPIV-seprase antibody E19, but was not labeled with anti-CD69 antibody FN50 (arrows). Similar results were obtained with anti-DPPIV-seprase antibody E26 (data not shown).

Thus, anti-DPPIV (anti-CD26) antibodies do not recognize the same epitope recognized by E19 and E26.

Figure 1: Activated T-Cells Exhibit both CD69 and CD26 (DPPIV) Antigens (Panel A) But Not the DPPIV Form Recognized by E19.

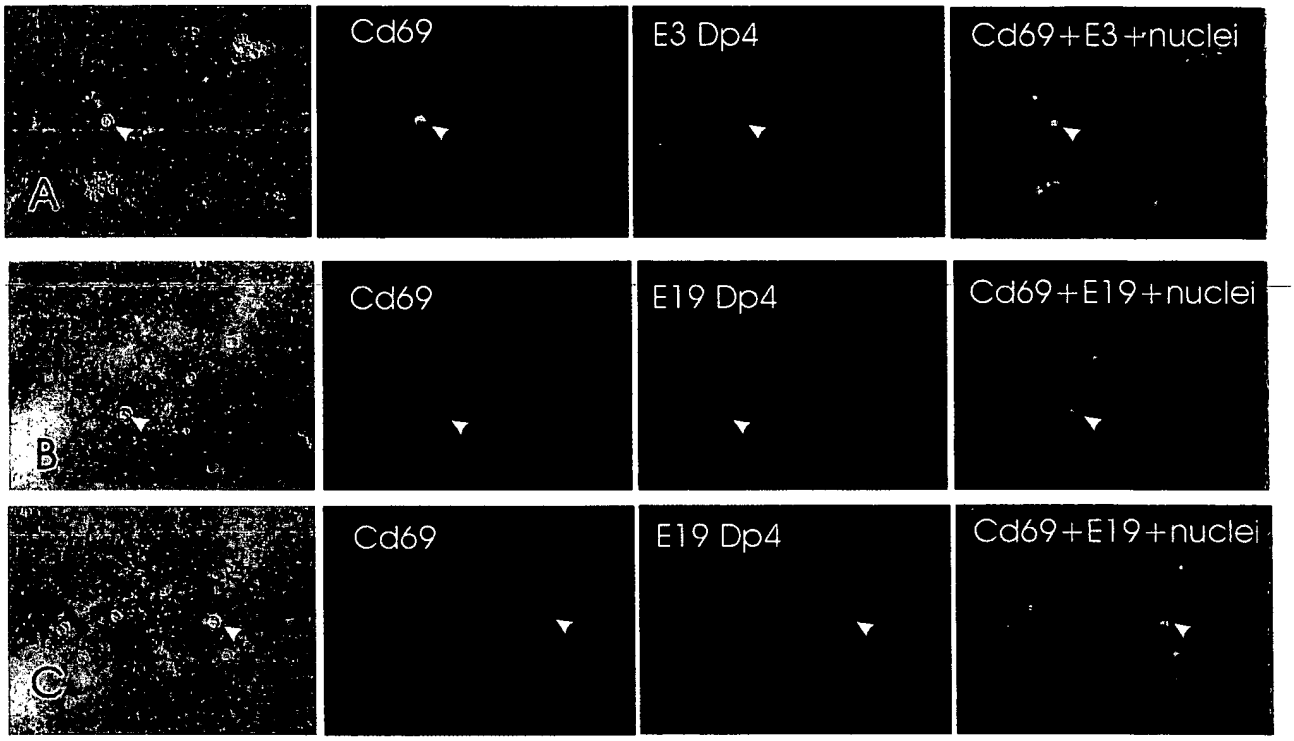

EXHIBIT 3

The DPPIV Form (Complex with Seprase) and Its Monoclonal Antibodies are Not Involved with Cellular Adhesion.

As DPPIV was has been reported to be an adhesion receptor for fibronectin (see Cheng et al., Johnson et al., Abdel-Shany et al. and Elble et al.). We examined if the DPPIV form recognized by E19 is involved with cellular adhesion (Ghersi et al. 2002, *J. Biol. Chem.* 277, 29231-29241).

WI38 human embryonic fibroblasts cells, $4x10^3$ per well (the number of cells in the area that remained attached and spread on 1.27 mm^2 areas of a microtiter well was counted), were seeded on surfaces in 96-well plates (Nunc, Inc., Naperville, IL), that were coated with rat tail type I collagen at the concentration of 600 μg/ml and followed by further coating with bovine serum fibronectin at the concentration of 100 μg/ml. Cells were seeded in the presence of mAbs at the concentrations indicated in figure 2. The wells that were not coated with protein were used as negative control. Type I collagen fibers were formed on the bottom of microtiter wells according to the procedure described.

Figure 2 shows that, mAb E19 (against DPPIV) does not affect cell spreading of WI38 human embryonic fibroblasts on fibronectin-coated collagen substratum (see figure 2a) and attachment to the fibronectin-coated collagen substratum (see figure 2b). Similar results were also obtained for E26 (data not shown). However, mAb C27 (against β1 integrins) inhibits WI38 cell spreading on and adhesion to fibronectin-coated collagen substratum, while mAb E19 (against DPPIV) or mAb C37 (anti-gp-90) do not (see figures 2a and 2b).

Thus, E19 and E26 do not inhibit binding of DPPIV form to fibronectin. Therefore, the epitope recognized by E19 and E26 differs from the anti-DPPIV antibodies in the cited art which reported inhibition of cell adhesion to fibronectin.

Figure 2: Attachment and Spreading of Human Cells on Fibronectin-Coated Collagen Substratum is not Mediated by the DPPIV Epitope Recognized by E19.